Quick guide

The Wnts

Joseph J. Loureiro

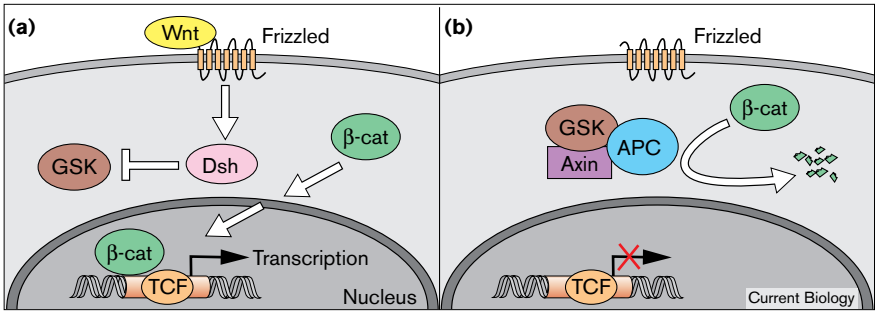
What are they? The Wnts (pronounced 'wints') make up a superfamily of secreted glycoproteins involved in cell–cell signaling.

How did they get that name? The name Wnt symbolizes the fusion of developmental biology with cancer biology. It is an amalgam of *wingless* (a *Drosophila* gene that is essential for embryogenesis, and the first member of the Wnt family to be discovered) and *int-1* (a murine proto-oncogene). Wnt proteins contain a conserved set of 22 cysteines as well as one or more *N*-linked glycosylation sites.

Their known functions are… Wnts direct cell fates. They have been implicated in diverse developmental decisions including the determination of tissue polarity and tissue induction.

Who are their known associates? Furious searches, using classical genetic approaches, repeatedly failed to turn up a Wnt receptor, the loss of which should have the same effect as does the loss of *wingless*. But investigators taking a biochemical approach identified a *Drosophila* gene, *D-frizzled2*, which allows previously unresponsive insect tissue culture cells to respond to a Wingless signal.

How do Wnts work? Developmental and cancer biologists have feverishly dissected the mechanism of Wnt signal transduction (see Figure; homologous vertebrate/invertebrate proteins are indicated in the legend). The prevailing dogma is that the Wnt signal causes β-catenin/Armadillo to accumulate in the nucleus where it acts together with the transcription factor TCF/LEF/Pangolin. But this might not be the whole story. In the developing chick limb bud, not all Wnts are sensitive to perturbations in β-catenin and TCF/LEF/Pangolin.



(a) The current view is that binding of Wnt/Wingless ligand to the Frizzled receptor activates the Dishevelled (XDsh/Dsh) protein. By some mysterious mechanism involving PDZ domains, Dsh inhibits GSK-3β/Zeste-white3. **(b)** In the absence of this inhibition, GSK-3β/Zeste-white3 (in conjunction with APC/D-APC and Axin) targets β-catenin/Armadillo (β-cat) for degradation by the proteosome. So, when the cell perceives Wnt/Wingless signal (a), β-catenin/Armadillo accumulates in the nucleus where it acts together with the DNA-binding protein TCF/LEF/Pangolin to stimulate transcription.

What do Wnts work on? Target genes for Wnt signaling include known modulators of cell fate, such as *Ultrabithorax* and *engrailed* in flies and *siamois* in frogs. One intriguing possible target is *E-cadherin*, a gene encoding a homophilic cell adhesion molecule that requires β-catenin/Armadillo for its function in regulating the actin cytoskeleton.

How do they travel between cells? It's not known, although genetic screens in *Drosophila* have identified enzymes required for Wingless signaling that modify extracellular matrix components. During certain stages of *Drosophila* development, the post-secretion movement or stability of Wingless is tightly regulated. The receptor D-frizzled might play a part in this process and a family of secreted Frizzled-like proteins (FRP/FrzB) that regulate Wnt ligand activity *in vivo* has recently been identified.

Where are they found? Everywhere except, so far, in fungi and plants. Their conservation among Chordates, Arthropods, Nematodes and Echinoderms suggests they have a pivotal role in multicellular animal life; the Wnt signal transduction pathway is also highly conserved among the animal phyla.

Most outrageous claim… Wnts could be the next cure for baldness. In transformed mice expressing a constitutively active form of β-catenin in their epidermis, there is evidence of excess hair follicle formation. But these mice also have a high incidence of skin tumors. Don't ask your dermatologist to genetically alter your scalp just yet.

Where can I find out more?

Wnt homepage at www.stanford.edu/~rnusse/
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Address: Department of Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3280, USA.